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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,043	10/21/2003	Matthias Mack	13235-014001	3494

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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,043	MACK ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 41-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/03, 3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 11 March 2004 has been entered in full. Applicant's election without traverse of Group II (claims 28-40, drawn to a method for reducing or depleting macrophages in a subject) in the reply filed on 14 August 2006 is acknowledged. Claims 1-27 and 41-52 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 14 August 2006. Claims 28-40 are under examination.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 21 October 2003 and 11 March 2004 were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent

application. 37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to sequences in Figure 15A-C, but does not identify the sequences by their sequence identifiers. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 30-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for substantially reducing or depleting macrophages in a subject, **wherein the subject has allergic asthma**, the method comprising.....**wherein said method substantially reduces or depletes macrophages in said subject**,

does not reasonably provide enablement for:

a method for substantially reducing or depleting macrophages in a subject, the method comprising.....".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that RANTES/CCL5 has been shown to bind and activate cells via CC chemokine receptor-1 (CCR1), CCR3, CCR4 and CCR5 (page 1). The specification states that a chimeric polypeptide (RANTES/PE38) directly targets, RANTES/CCL5 responsive cells (CCR5 expressing cells) that regulate the recruitment of CCR4/CCR8-expressing cells into allergen-challenged lungs. RANTES/PE38 is a chimeric protein comprising RANTES/CCL5 fused to pseudomonas exotoxin A (PE38). RANTES/CCL5 binds to CCR5 and the toxin is internalized through the receptor (Figure 14). The chimeric polypeptide is believed to reduce the accumulation of CCR5(+) cells and/or macrophages (page 2, lines 1-9). The specification teaches that reducing or preventing the early accumulation of macrophages in the lung tissue can reduce the early elements of asthma (page 3, lines 11-31 and page 9, lines 10-25). The specification teaches the administration of RANTES/PE38 to a mouse model for allergic airway disease. The specification teaches the reduction of F4/80+ macrophage

population upon the administration of RANTES/P38 in the mouse model (page 40, lines 20-31 and Figure 16).

The instant claims are not supported by an enabling disclosure because the specification fails to teach the reduction/depletion in subject suffering from any disease including atherosclerosis or multiple sclerosis, upon the administration of the claimed product. Clerin *et al.* (Circulation, Vol. 110, No. 17, Suppl. S. page 177, November 2004) teach the use of an animal model for atherosclerosis. Apolipoprotein E deficient mice were used as a model of atherosclerosis. Clerin *et al.* teach the reduction of monocytes/macrophages infiltrate into the aortic wall upon administration of P-selectin antagonist WAY-197697. Howard *et al.* (The Journal of Clinical Investigation, Vol. 103/2 pages 281-290, January 1999) teach the use of an animal model for multiple sclerosis. Relapsing experimental autoimmune encephalomyelitis (R-EAE) is a Th1-mediated autoimmune demyelinating disease of the central nervous system (CNS), which serves as a useful model for multiple sclerosis (MS) (page 281, 1st paragraph). Howard *et al.* teach that blockage of a CD40/CD154 inhibits early events in MS. CD40 receptor is expressed on macrophages (page 281-page 282, 3rd paragraph). Howard *et al.* teach that anti-CD154 antibodies diminished CNS immune cell infiltration. Howard *et al.* teach that anti-CD154 antibodies may prevent activated myelin-specific T cells and/or macrophages from entering the CNS or from being retained in the target organ (page 283, last paragraph-page 284 and Figure 2). Both references teach the use of proper animal models to examine the effects of administered compositions and macrophage activity. Both references employ proper experiments to determine macrophage activity

(i.e. histological analysis of aortic walls for atherosclerosis and histological analysis of spinal cord sections for multiple sclerosis). The instant specification does not disclose working examples demonstrating reduction/depletion of macrophages is a subject suffering from any type of disease including atherosclerosis or multiple sclerosis, upon the administration of the claimed product. It fails to disclose proper animals models and experiments for the scope of the instant claims. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether the claimed product could reduce/deplete macrophages in a subject suffering from any disease. Lastly, the instant claims are not supported by an enabling disclosure because they fail to teach the *dose effective* to reduce/deplete macrophages in a subject. Thus the claims as recited read on administering trace amounts of the claimed composition instead of dosages that are effective to achieve the goal.

Due to the large quantity of experimentation necessary to reduce/deplete macrophages in a subject suffering from any type of disease/condition comprising administering an effective dose of the claimed composition, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite limitations regarding effective dosages and the diseases/conditions wherein macrophages can be depleted, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are indefinite because they must achieve the goal stated in the preamble. The claims do not have a step that clearly relates back to the preamble.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28, 29, 32-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruhl *et al.,* Journal of Immunology 166:2420-2426, 2001 (reference submitted by Applicant) in view of Schuh *et al.,* Faseb J 16:228-230, Feb. 2002 (reference submitted by Applicant) and Blease *et al.,* Journal of Immunology 167:6583-6592, 2001 (reference submitted by Applicant).

The instant claims are drawn to a method for substantially reducing or depleting macrophages in a subject, the method comprising:(a) identifying a subject in need of reducing macrophages and (b) administering to the subject a pharmaceutical composition comprising a chimeric polypeptide that comprises a first polypeptide domain comprising at least one moiety that specifically binds to a CCR5; and a second polypeptide domain comprising at least one of (a)-(d):(a) a moiety that binds to a T cell surface polypeptide..or (d) a cell toxin.

Bruhl *et al.* teach the construction of a bispecific single-chain antibody directed against CCR5 and CD3, called anti-CCR5-anti-CD3-bispecific ab (page 2421 and page 2422, Results, first paragraph). Bruhl *et al.* teach the depletion of CCR5-positive primary cells using anti-CCR5-anti-CD3-bispecific ab (page 2422, last paragraph and Figure 5). Bruhl *et al.* teach that CCR5 is expressed on monocytes/macrophages and T cells (page 2425)(**applies to claims 28, 33, 35**). Bruhl *et al.* teach the recombinant construction of a chimeric fusion protein comprising RANTES protein and a truncated version of a cell toxin, *Pseudomonas* exotoxin (RANTES-PE38) (page 2421 and page

2423, last paragraph)(**applies to claims 28, 33, 34, 36, 37**). Bruhl *et al.* teach that the RANTES-PE38 fusion protein binds to CCR5 and down modulates the receptor from the cell surface and that RANTES-PE38 fusion protein destroys CCR5-positive CHO cells (abstract, page 2424 and Figures 8-9). Bruhl *et al.* teach that the construct efficiently depletes CCR5 positive cells and appears useful as an agent in the treatment of chronic inflammatory disease and is a promising candidate as a therapeutic agent (abstract; page 2421, 2nd column, lines 1-3 and page 2425, last paragraph). Bruhl *et al.* do not teach the administration of a composition comprising a chimeric polypeptide that comprises a first polypeptide domain comprising at least one moiety that specifically binds to a CCR5 and a second polypeptide domain comprising a moiety that binds to a T cell surface polypeptide or a cell toxin.

Schuh *et al.* examine the role of chemokine receptor CCR5 and its ligand, RANTES, in an animal model for chronic fungal asthma induced by an intrapulmonary challenge with *Aspergillus fumigatus* conidia (abstract). Schuh *et al.* teach that RANTES has been linked with both atopic and nonatopic asthma. Schuh *et al.* teach a correlation between CCR5 and allergic asthma. Individuals who are homozygous for the coding sequence of CCR5 are highly resistant to asthma (page 228, 5th paragraph). Schuh *et al.* teach that while the lack of CCR5 markedly restricted the development of fungal asthma, the neutralization of RANTES (via administered anti-RANTES antibodies) further reduced the hallmarks of allergic asthma in the mouse model. Schuh *et al.* teach that CCR5 and RANTES are key contributors to the development and maintenance of

chronic fungal asthma in the mouse model (page 229, Figure 3 and page 230, last paragraph).

Blease *et al.* teach that IL-13 contributes to allergic and asthmatic responses and represents an attractive target in theses diseases (abstract). Blease *et al.* teach that a strategy for targeting IL-13 receptor positive cells during that involves the use of a chimeric fusion protein comprising IL-13 and Pseudomonas exotoxin called IL-13-PE38QQR (page 6583, 2nd paragraph). Blease *et al.* target IL-13 responsive cells in the lung via intranasal administration of IL-13-PE38QQR in an allergic airway disease mouse model. Chronic fungal-induced allergic airway sensitized mice received IL-13-PE38QQR intranasally on the 14th day after challenge concluding on day 28 (page 6584, 1st paragraph). The IL-13-PE38QQR fusion protein ameliorated chronic fungal-induced allergic airway disease in the mouse model (abstract). Blease *et al.* teach that IL-13-PE therapy reduced airway hyperresponsiveness during chronic fungal induced allergic airways.

Schuh *et al.* and Blease *et al.* do not teach a method wherein the composition is administered in a regimen of a short course or beginning at the time of exposure, after the time of exposure or prior to impending exposure (**claims 38 and 39**). However, adjustments of the timing of pharmaceutical drug administration are deemed merely a matter of judicious selection and routine optimizations, which is well within the purview of the skilled artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the anti-CCR5-anti-CD3-bispecific ab or the chimeric fusion

protein RANTES-PE38 to deplete CCR5 expressing cells as taught by Bruhl *et al.* in a method for reducing/depleting macrophages in a human suffering from allergic asthma with a reasonable expectation of success. The motivation and expected success is provided by Bruhl, Schuh and Blease. Bruhl *et al.* teach that anti-CCR5-anti-CD3-bispecific antibodies and RANTES-PE38 fusion protein efficiently depletes CCR5 positive cells and that CCR5 is expressed on monocytes/macrophages. Schuh *et al.* teach that CCR5 and RANTES are key contributors to the development of chronic fungal asthma and administered anti-RANTES antibodies reduced the hallmarks of allergic asthma in a mouse model for chronic fungal asthma. Blease *et al.* demonstrate that a chimeric fusion protein comprising IL-13 and Pseudomonas exotoxin (IL-13-PE38QQR) can be administered intranasally and reduce chronic fungal-induced allergic airway disease a mouse model. It would make it obvious to employ the claimed method in humans because Bruhl *et al.* teach the depletion of macrophages and that RANTES-PE38 fusion protein is a useful agent in the treatment of chronic inflammatory disease and Schuh et al., who teach the successful treatment (reduction of peribronchial cell infiltrates) in an animal asthma mouse model upon administered anti-RANTES antibodies.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
10/24/06

MARIANNE P. ALLEN
PRIMARY EXAMINER
10/25/06
AU1647